REMARKS

This Amendment, filed in reply to the Office Action dated November 25, 2009, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 9 and 10 are rejected. Claims 9 and 10 are amended herewith to recite a method for treating a herniated disc or herniated pulposus "in a mammal." Support for this amendment can be found throughout the specification as originally filed, and at, for example, page 4, lines 6-9, and in working Examples 2 and 3.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Claim 9 is Patentable Under 35 U.S.C. § 102(b)

On page 2 of the Office Action, Claim 9 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Haro *et al.* (*Journal of Clinical Investigation*, 2000, 105(2):143-150; hereinafter "Haro #1"), essentially for the reasons set forth on page 3 of the Office Action mailed April 17, 2009. The Examiner contends that Applicants' previous arguments over Haro #1 are unpersuasive, for the following reasons.

First, the Examiner sustains the rejection, in part, on the basis that the specification as filed fails to provide a specific definition for the phrase "consisting essentially of," or a definition of what constitutes the basic and novel characteristics of the claimed invention; in view of such, the Examiner considers it proper to construe the term "consisting essentially of" in Claim 9 as

"comprising," citing *PPG Industries v. Guardian Industries*, 156 F.3d at 1355 (Fed. Cir. 1998) in support. On this rationale, the Examiner contends that the scope of Claim 9 encompasses any additional element or step, including the MMP-$3^{-/-}$ macrophages in the composition administered in the *in vitro* method of Haro #1.

Second, the Examiner contends that, even assuming *arguendo* the specification describes the basic and novel characteristics of the claimed invention so as to exclude macrophages, the rejection is proper, stating that "although the MMP-7 [in the method of Haro #1] is derived from macrophages, *there is no requirement that the MMP-7 need be generated at the site of HNP*; rather, all that is required is that MMP-7 be present. The presence of macrophages and chondrocytes, and the interactions among them … can be supplied by the host … [e]xogenous administration of MMP-7 would accomplish the same results as disclosed in Haro *et al.*" (Emphasis added.)

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

First, Applicants respectfully disagree that, absent an express definition in the specification of what the phrase "consisting essentially of" encompasses, or an express definition of what constitutes the "basic and novel characteristics of the claimed invention," the recitation "consisting essentially of" in Claim 9 is properly construed as "comprising," *i.e.*, to encompass any and all additional steps or elements. Specifically, neither the statute, nor settled law, requires an *explicit* definition in the specification of the "basic and novel characteristics of the claimed invention," or of the term "consisting essentially of," before the phrase "consisting

essentially of" shall be afforded its proper meaning (*i.e.*, a middle ground between "comprising" and "consisting of," permitting the inclusion of components not listed in the claim "provided they do not materially affect the basic and novel properties of the claimed invention," *In re Janakirama-Rao*, 317 F.2d 951, 954 (C.C.P.A. 1963)), as the rejection appears to posit.

As evidence, in *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1240-1241 (Fed. Cir. 2003), the court, in determining what properties were "basic and novel" to the invention at issue, held that good wetting of the claimed alloy steels was undoubtedly a basic and novel property of the invention, because the specification stated such as a *goal of the invention*. Likewise, Applicants respectfully submit that, in light of the claim language and the description in the "disclosure of the invention" section of the instant specification, those of skill in the art would readily appreciate herniated disc resorption as a basic and novel property of the claimed method, being a stated goal of the invention. Accordingly, additional elements that materially affect herniated disc resorption are excluded by recitation of the phrase "consisting essentially of" in Claim 9, such as macrophages.

Specifically, as noted previously by Applicants, the MMP-$3^{-/-}$ macrophages administered to the vertebral disc in the *in vitro* method of Haro #1 undoubtedly materially affect herniated disc resorption; indeed, in the method of Haro #1, the addition (and subsequent infiltration) of these macrophages is absolutely required for disc resorption in the method of Haro #1. Such is evidenced at least by the demonstration in Haro #1 that inhibition of infiltration of wild-type macrophages (*i.e.*, MMP-7 producing macrophages) into the disc, by adding neutralizing antibody to TNF-α, precluded disc resorption. *See* page 147, the paragraph bridging columns 1

and 2, of Haro #1. *See also* page 2, 1st paragraph, of the Rule 132 Declaration submitted herewith, executed by the Hirotaka Haro, the author of Haro #1.

The rejection posits the MMP-$3^{-/-}$ macrophages "consist essentially of" MMP-7,[2] such that administration of MMP-$3^{-/-}$ macrophages from MMP-3 null mice to a vertebral disc *in vitro* in the method of Haro #1 anticipates Claim 9. However, as expressly acknowledged in Haro #1, because the macrophages are *absolutely required* for disc resorption therein, the method of Haro #1 does not constitute administering a composition *consisting essentially of* MMP-7, as claimed. Applicants submit that Haro #1 does not anticipate the subject matter of Claim 9 for at least this reason.

Second, Applicants respectfully disagree that, even if the specification did expressly define that macrophages were excluded by the term "consisting essentially of," Haro #1 would anticipate the subject matter of Claim 9, as the rejection posits. *See* page 3, 2nd paragraph, of the outstanding Office Action. In this section, the Examiner contends that "although the MMP-7 [in the method of Haro #1] is derived from macrophages, there is no requirement that the MMP-7 need be generated at the site of HNP … all that is required is that MMP-7 be present[; the] presence of macrophages and chondrocytes, and the interactions among them, which Applicant asserts is required for HNP resorption, can be supplied by the host." (Emphasis added.) Notwithstanding the absence of any evidentiary support to support such an assertion, even assuming *arguendo* such were true, anticipation requires that each and every element of the claimed invention be *disclosed* within a single reference, either expressly or inherently, arranged

[2] See page 4, 3rd paragraph, of the Office Action mailed April 17, 2009.

as in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452 (Fed. Cir. 1984) (citing *Connell v. Sears, Roebuck and Co.*, 722 F.2d 1542 (Fed. Cir. 1983). See also, *Net MoneyIn, Inc. v. Verisign, Inc.*, 2008 U.S. App. LEXIS 21827, 1, 27 (Fed. Cir. 2008) (In order to anticipate a claim under 35 U.S.C. § 102, a reference must disclose within the four corners of the document not only all of the elements claimed but also all of the elements arranged or combined in the same way as recited in the claim). Thus, the pertinent issue is what Haro #1 discloses. Haro #1 does not disclose *any* method wherein macrophage-chondrocyte interactions, leading to macrophage infiltration and disc resorption, are "supplied by the host," because no such "host" exists in the method of Haro #1. Rather, the method of Haro #1 is performed *in vitro*, using isolated intervertebral discs, to which isolated MMP-$3^{-/-}$ macrophages are administered; there are no "host" macrophages to either supply TNF-α, or to mediate disc infiltration in the method of Haro #1, as is asserted in the rejection.

Accordingly, because Haro #1 fails to disclose *any* method wherein macrophages are supplied by a "host" in addition to administration of the MMP-$3^{-/-}$ macrophages, and because Haro #1 expressly acknowledges that macrophages are required for disc resorption in the assay therein, MMP-$3^{-/-}$ macrophages in the method of Haro #1 clearly materially affect a basic and novel property of the invention, such that the method of Haro #1 is excluded from the scope of Claim 9.

Nevertheless, in the interest of advancing prosecution, and without acquiescing to the merits of the rejection, Claim 9 is amended herewith to recite that MMP-7 is administered to the affected site "in a mammal." Haro #1 only discloses *in vitro* assays, and does not disclose, either

expressly or inherently, the administration of MMP-7, or MMP-$3^{-/-}$ macrophages, to a mammal. Accordingly, Haro #1 does not anticipate Claim 9 as amended for at least this reason also.

Withdrawal of the rejection is respectfully requested.

Claim 10 is Patentable Under 35 U.S.C. § 103(a)

On page 4 of the Office Action, Claim 10 is rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Haro #1, essentially for the same reasons as set forth on page 4 of the Office Action mailed April 17, 2009.

In maintaining the rejection, the Examiner again acknowledges that Haro #1 fails to disclose a method consisting of administering MMP-7 and pharmaceutically acceptable carrier to the affected site of a herniated disc or herniated nucleus pulposus. However, the Examiner continues to allege that those of ordinary skill in the art would understand from the statement in Haro #1 that "[m]acrophage-derived MMP-7, but not MMP-3, was required for disc resorption and macrophage invasion of disc tissue" that no additional components, such as the macrophages themselves administered in the method of Haro #1, are required for disc resorption. On this basis, the Examiner takes the position that those of ordinary skill in the art would readily have administered *just* MMP-7 to the site of a herniated disc.

Second, noting that Haro #1 discloses that herniated discs may resolve spontaneously through infiltration of host macrophages, the rejection also appears to be sustained on the allegation that "[t]here is no basis to believe that administration of MMP-7 in a pharmaceutically acceptable carrier would preclude this infiltration … [and as] such, the allegedly critical

macrophage/chondrocyte interaction can be accomplished by host cells." (Emphasis added.) In response to Applicants' previous argument that administering MMP-7 alone in the *in vitro* method of Haro #1, instead of MMP-$3^{-/-}$, would render the method of Haro #1 unsuitable for its intended purpose, the Examiner appears to find such unpersuasive, stating that "Applicants have provided no evidence why administering MMP-7 alone [in the method of Haro #1] would be inoperable."

Third, the Examiner appears to dismiss Applicants' previous persuasive demonstration of unexpected results as being irrelevant to the rejection at hand, because MMP-3 "[was not] utilized as a reason to reject Claim 10, other than to demonstrate that it is MMP-7, rather than MMP-3 that is required for resorption."

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

First, Applicants respectfully disagree that those of ordinary skill in the art would understand from the recitation in Haro #1 that "[m]acrophage-derived MMP-7, but not MMP-3, was required for disc resorption and macrophage invasion of disc tissue" that MMP-7 alone would be sufficient for herniated disc resorption. As explained by Hirotaka Haro in the attached Rule 132 Declaration, the author of Haro #1, Haro #1 discloses that in the disclosed method therein, it is the MMP-$3^{-/-}$ macrophages, when administered to the isolated intervertebral disc *in vitro*, that mediate its resorption, not MMP-7 alone. *See* page 2, 1st paragraph, of the Rule 132 Declaration. This is experimentally demonstrated in Haro #1 by inhibition of infiltration of wild-type macrophages (*i.e.*, MMP-7 producing macrophages) into the disc by adding neutralizing

antibody to TNF-α, which precluded disc resorption. *See* page 147, the paragraph bridging columns 1 and 2, of Haro #1. In this regard, Applicants respectfully submit that the portion of Haro #1 relied upon to support the rejection is taken out of context, being relied upon for the proposition that it "removes the requirement of additional components for treating HNP." However, as would be recognized by those of ordinary skill in the art, Haro #1 explicitly discloses the criticality of several other elements, including chondrocyte-produced MMP-3, soluble TNF-α, chemotactic factor production, and *macrophage infiltration*, for disc resorption. Because of the criticality of these additional elements in the *in vitro* method of Haro #1, Applicants respectfully submit that those of ordinary skill in the art would not have possessed any motivation to administer MMP-7 without macrophages in the method of Haro #1, nor possessed any expectation of success in doing so. While the Examiner contends that there is no evidence that omitting macrophages from the method of Haro #1 would prevent disc resorption in the method of Haro #1, such evidence is rife in Haro #1. *See* page 147, the paragraph bridging columns 1 and 2, of Haro #1.

Second, Applicants respectfully disagree that those of ordinary skill in the art at the time of the invention, aware that herniated discs *in vivo* may resolve *spontaneously* through macrophage infiltration, would readily have administered MMP-7 alone because it would not have "preclude[d] this macrophage infiltration." That those of ordinary skill in the art might understand that administration of MMP-7 would not *preclude* normal infiltration of host macrophages into a herniated disc (to promote resorption) does not, in itself, provide *any* reason for one of ordinary skill in the art to actively administer MMP-7. To sustain a finding of

obviousness, a credible reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does must be made explicit. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). Simply because MMP-7 would not have an inhibitory effect on the spontaneous resorption of herniated discs is not a reason that would have prompted a person of ordinary skill in the relevant field to *actively administer* MMP-7 to the affected site of a herniated disc in a patient. Indeed, in view of the arguments on page 3 of the Office Action, wherein it is asserted that "host macrophages provide MMP-7" and that "[t]he presence of macrophages and chondrocytes, and the interactions among them … can be supplied by the host," it is difficult to reconcile why those of ordinary skill in the art, who allegedly recognized that all the elements and critical macrophage-chondrocyte interactions necessary for disc resorption can be supplied by the host, would have possessed any reason whatsoever to administer additional MMP-7 to such host.

Nevertheless, even assuming *arguendo* that those of ordinary skill in the art, in view of Haro #1, would readily have administered MMP-7 alone *in vivo*, with an expectation that the naturally-occurring macrophage-mediated disc resorption process would not be precluded, Applicants note that methods consisting of, or consisting essentially of, administering MMP-7 to the affected site of a herniated disc in a mammal are unexpectedly superior with respect to disc resorption vis-à-vis the methods in the prior art. For example, Haro #1 only discloses the natural, spontaneous resorption of discs *in vivo* via macrophage infiltration, and reconstruction of this process *in vitro* by administering macrophages. However, as noted in the attached Rule 132 Declaration, spontaneous resorption of herniated discs by macrophage infiltration takes several

months. *See* page 2, 2nd paragraph and accompanying illustration, of the attached Rule 132 Declaration. In contrast, however, the Rule 132 Declaration experimentally demonstrates that when MMP-7 was administered alone to the site of a hernitated disc in a mammal, a decrease in the nucleus pulposus was observed by just 1 week post-administration, and that this effect was independent of macrophage infiltration. *See* page 4, and the accompanying table, on page 4 of the attached Rule 132 Declaration. This method is also unexpectedly superior over other protease-based therapies known in the art, such as chymopapain, as it preserves chondrocyte function, which in turn sustains the regenerative capacity of the disc. *See* page 3, paragraphs 4-5, of the attached Rule 132 Declaration.

Lastly, while the Examiner considers Applicants' previously persuasive evidence of the unexpectedly superior disc resorption upon administration of MMP-7 vis-à-vis MMP-3 (*i.e.*, Haro *et al.* (*Spine*, 1997, 22(10):1098-1104)) to be irrelevant in view of the instant rejection, *see* page 5, 2nd paragraph, of the outstanding Office Action, Applicants respectfully submit that such evidence remains highly relevant; a showing of superior properties over the prior art to rebut an obviousness rejection requires only a comparison with the *closest* prior art, not that of the Examiner's choosing. *See In re Holliday*, 584 F.2d 384, 386 (C.C.P.A 1978). Thus, that Haro *et al.* is no longer relied upon to support the rejection, because Applicants showing of unexpected results over such art was persuasive, does not negate the fact that Applicants have already provided on the record a persuasive showing of unexpected results vis-à-vis the closest prior art, which is all the law requires. *Holliday*, 584 F.2d at 386.

In view of the foregoing, Applicants respectfully submit that the presently claimed invention is nonobvious, and patentable.

Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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Date: May 20, 2010